REMARKS

The amendments to the specification are being made to correct typographical errors in the citations of references.

Favorable consideration and early allowance are respectfully solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Allen C. Yun
Registration No. 37,971

ACY:pr
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
F:\,C\cohn\moroz3\pto\2nd PA.wpd

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning at the bottom of page 1, line 14, has been replaced with the following rewritten paragraph:

The name "*ferritin*" actually encompasses a number of individual isomeric forms which are characteristic of different tissue types. Each isoferritin has 24 subunits of two distinct types, being light subunits (L) and heavy subunits (H). These subunits differ in molecular weight, the light subunit being about 18 kDa, and the heavy subunit about ~~1~~9-21 kDa. The isoferritins extracted from different tissues or organs typically exhibit different isoelectric points, with the isoelectric focusing pattern of human tissues forming a continuous spectrum: those tissues associated with high iron storage have ferritin at the basic end of the spectrum (e.g. spleen and liver), while iron poor tissues, (e.g. heart and placenta) and malignant cells have acidic ferritin. (Drysdale, J., *Ciba Found. Symp.*, **51**:41, 197~~7~~6). The difference in isoelectric point appears to be related to the different distribution of light and heavy subunits in each type. Specifically, heavy subunit-rich ferritin are relatively acidic, and light chain rich ferritin are relatively basic (~~Cosell~~Covell, et al., in *Ferritin and Isoferritins as Biochemical Markers*, p. 49-65, 1984, Elsevier). Current studies indicate that the H and L subunits are encoded by a complex group of genes.

The paragraph beginning at page 2, line 13, has been replaced with the following rewritten paragraph:

A specific type of acidic isoferritin has been shown to be characteristic of neoplastic cells and placental cells (Drysdale and Singer, *Cancer Res.*, **~~4434~~**:3352, 1974). This protein is also known as oncofetal ferritin or placental isoferritin (PLF). Human placental ferritin has been shown to be composed predominantly of a single subunit type comigrating with a liver ferritin standard on SDS-PAGE (Brown et al., *Biochem. J.*, **182**:763, 1979). However, an immunoradiometric assay performed with anti-human spleen ferritin has shown tissue specific antigenicity for PLF (Brown et al., *supra*). A three subunit structure has been revealed for PLF (Moroz et al., *G. I. Pat. Clin.*, **1**:17-23, 1986). In addition to the L and H subunits characteristic of all ferritin, there is also a high molecular weight (43 kDa) subunit which appears to be unique for human placenta, and thus provides a potential site for identification of the placental isoferritin molecule as distinguished from any other type of ferritin.

The paragraph beginning at the bottom of page 2, has been replaced with the following rewritten paragraph:

Various ferritin isoforms have been isolated from normal and malignant tissues, the most acidic ones predominating in tumor and fetal tissues (Drysdale J., 1976, *Ciba Found. Symp.* **51**:41; *Arosio et al., J. Biol. Chem.*, **253**:4451, 1978). It has

been suggested that the assay or acidic isoferritin in the serum may be of value in the diagnosis of malignancy (Hazard *et al.*, *Nature*, **265**:755, 1977). Elevated concentrations of serum ferritin were found in patients suffering from a variety of malignant diseases, including acute lymphocytic leukemia (ALL) (Matzner *et al.*, *Am. J. Hematol.*, **9**:13, 1980), hepatoma (Giannoulis, *Digestion*, **30**:236, 1976~~7~~84) and recently Hodgkin's disease (Bezwoda *et al.*, *Scand. J. Haematal.*, **35**:505, 1985). In assays based on antibodies HeLa cell ferritin, Hazard and Drysdale found higher concentrations of ferritin in sera from patients with various tumors than in the same sera assayed by antibodies directed against normal liver ferritin (Hazard *et al.*, *supra*). Others have failed to demonstrate a consistent pattern of isoferritins in tumor tissues (Cragg *et al.*, *Br. J. Cancer*, **35**:635, 1977; Halliday *et al.*, *Cancer Res.*, **36**:4486, 1976) or in sera obtained from patients with tumors (Jones *et al.*, *Clin. Chim. Acta.*, **85**:81, 1978; Jones *et al.*, *Clin. Chim. Acta.*, **106**:203, 1980).

The paragraph beginning at the bottom of page 3, has been replaced with the following rewritten paragraph:

Breast cancer is a malignant disease effecting different populations at a rate of one to every 9-13 of women. Early diagnosis of breast cancer is known to considerably improve the prognosis of the patient. Diagnosis of breast cancer is based today mainly on imagining techniques such as mamma graphs

verified at times by biopsies. Blood-based assays of breast cancer have been reported in the literature, for example, biomarker such as CA 15.3 (Daly, L. *et al., Comparison of a novel assay for breast cancer mucin to and CA 54 15.3 carcinoembryonic antigen, J. Clin. Oncol.*, **10**:1057-65, 1992); the CA 549(2) marker (Dormers, I. J., *et al.*, CA 549; a new tumor marker for patients with advanced breast cancer *J. Clin. Lab. Anal.*, **2**:168-73, 1988); and the marker CA M29 CEA (Duistrian, A. M. *et al., Evaluation of CA M26, CA M29, CA 15.3 and CEA as circulating tumor markers in breast cancer patients. Tumor Biol.*, **12**:82-90, 1991). However these assays, reported in the scientific community have not gained, to date, clinical significance (Werner M., *et al., Clinical utility and validation of emerging biochemical markers from mammary adenocarcinoma, Clin. Chem.*, **39/11**(B):2386-96, 1993).